UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/524,044	12/12/2005	Laurent Meijer	BJS-1721-86	4404

23117 7590 12/23/2008

NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
MANOHAR, MANU M	
ART UNIT	PAPER NUMBER
1617	
MAIL DATE	DELIVERY MODE
12/23/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,044	MEIJER ET AL.	
	Examiner	Art Unit	
	MANU MANOHAR	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) *13,21,24,27 and 33-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,14-20,22,23,25,26,28-32 and 38-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02/08/2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/08/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The status of the Claims

Claims 1- 43 are pending in the application. Original claims 1-43 were subjected to restriction and election of species. The details are below.

Election and Restriction

Applicant's election of Group I in the reply filed on September 23, 2008 is acknowledged. The applicants elected a species, a compound 39, stated in page 24, line 2 of the specification. **Applicant stated that claims 1-12, 14-20, 22, 23, 25, 26, 28-32 and 38-43 are believed to read on the elected species. Claims 13, 21, 24, 27 and 33-37 are not directed towards the elected species hence these claims are withdrawn from the consideration.** The elected species, compound 39 found to be free of prior art. Hence the generic structure of formula 1 of claim 1 is considered in this office action and the prior art search was expanded to genus. Election was made without traverse in the reply filed on September 23, 2008.

Priority

This application has the filing date of December 12, 2005 and is a national stage application of PCT/EPO3/09515 with a filing date of August 08, 2003 and claims the benefit of European Patent Office application (EPO) 02292019.3 with the filing date of

August 09, 2002. **This application is considered with the priority date of August 09, 2002.**

Information Disclosure Statement

The information disclosure statement filed on Feb 08, 2005 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. Foreign patent documents and non-patent literature have been listed in IDS but the applicant failed to provide a copy of each publication.

Drawings

The drawings are objected to because there no description of drawings in the application. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the

renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12, 14-20, 22, 23, 25, 26, 28-32 and 38-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is drawn to the structure of a chemical formula I . The structure of the chemical formula I is not drawn correctly and the double bond for Nitrogen atom between the position 5 and 6 do not comply with standard chemical structure. Claims 2-12, 14-20, 22, 23, 25, 26, 28-32 and 38-43 which read on the instant claim are also rejected.

Claims 16 - 20, 23, 25, 26, 28-32 recite the limitation R group in the formula of claim I. There is insufficient antecedent basis for this limitation in the claim. The substituent R group is missing in the formula I.

Claims 42 and 43 recite the broad recitation 100 to 1000mg, and the claim also recites 'preferably' 300 to 600mg which is the narrower statement of the range/limitation. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 39 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating neurodegenerative disorders such as Alzheimer's disease does not reasonably provide enablement for preventing neurodegenerative disorders. The specification does not enable any person skilled in

the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). These include: (1) breadth of the claims; (2) nature of the invention; (3) state of the prior art; (4) amount of direction provided by the inventor; (5) the level of predictability in the art; (6) the existence of working examples; (7) quantity of experimentation needed to make or use the invention based on the content of the disclosure; and (8) relative skill in the art. All of the factors have been considered with regard to the claim, with the most relevant factors discussed below:

1) The breadth of claims: Claim 39 is directed to the pharmaceutical composition for treating or preventing neurodegenerative disorders such as Alzheimer's disease and Parkinson's diseases. This claim is too broad and it is not supported by the specification. The prevention of neurodegenerative disease is a very broad claim. It is known that neurological disorders are diverse in nature and varied in the origin. Some neurological disorders are treatable to certain extent but these neurological disorders are not preventable as claimed. It is clear to a person skilled in this art that each neurodegenerative disorder is distinct and varied in origin and distinct in the way of manifestation. Most of these diseases are not preventable none of the diseases have been prevented with a single compound as claimed here.

2) The nature of the invention: The invention is drawn to the pharmaceutical compositions containing pyrrolo-pyrazines derivative having inhibitory activity to kinase

enzymes which can be applied to the biological systems. The instant claim is directed to preventing neurodegenerative disorders such as Alzheimer's diseases.

3) The state of the prior art: The state of the art is high when the claims address preventing varied neurodegenerative disorders. Although there are number of publications describing methods of treating neurological disorders with compounds and compositions there is no evidence in the prior art that the instant composition would prevent Alzheimer's and Parkinson's diseases. In the absence of further guidance, undue experimentation would be required by one skilled in the art to use the claimed method to prevent neurological disorders.

4) The amount of direction provided by the inventor: There is nothing in the specification that would indicate that the current invention prevents neurodegenerative diseases. The prevention of neurodegenerative disease is a very broad claim. General guidance for preparing a pharmaceutical composition with comprising the derivatives of pyrrolo-pyrazine as an active principle with a nonspecific pharmaceutically acceptable carrier is given (Page 10 of the specification). With respect to the treatment the specification state the composition can be given in the form of oral, topical or by injection. However there are no specific directions for prevention about the formulation for the different doses and subject population. Consequently, a burdensome amount of research would be required by one of ordinary skill in the art to practice the invention.

5) Predictability of the art: The art is unpredictable when the claim addresses preventing the neurodegenerative disorders. Although there are several studies regarding the treatment of neurological disorders there are no evidences in the literature

that state that any compound including the instant compound that would prevent Alzheimer's and Parkinson's diseases. In the absence of further guidance, undue experimentation would be required by one skilled in the art to use the claimed method to prevent neurological disorders.

6) The presence or absence of working examples: Applicant describes several experiments in the instant specification related to chemistry and cell biology. These experiments illustrate the activity of kinases and the inhibition of the kinases with the derivatives of pyrrolo-pyrazine derivatives. However the specific working examples are lacking in the specification. Particularly there are no examples for the prevention and treatment of neurodegenerative disorders such as Alzheimer's diseases. What is provided in the specification is a method of making a composition and use as inhibitor of enzyme kinases. There are no working examples of the specific formulation and administration for prevention. Therefore, the practitioner would turn to trial and error experimentation to make/use the instant compositions for preventing neurodegenerative disorders without guidance from the specification or the prior art.

7) The quantity of experimentation: One skilled in the art would be required to undertake undue experimentation to make and/or use the invention as claimed. First the subject matter of prevention is not established. It is not clear about methodology of identifying the subject who can be prevented from the neurodegenerative diseases. The specification does not provide enough guidance. Also there is a lack of methodology to establish that the subjects are prevented from the neurodegenerative disease by the administration of the instant composition as well as the end point of

prevention regime. Thus without undue experimentation one skilled in the art would not be able to practice this invention for preventing neurogenerative disorders like Alzheimer's and Parkinson's diseases.

Claim 40 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). These include: (1) breadth of the claims; (2) nature of the invention; (3) state of the prior art; (4) amount of direction provided by the inventor; (5) the level of predictability in the art; (6) the existence of working examples; (7) quantity of experimentation needed to make or use the invention based on the content of the disclosure; and (8) relative skill in the art. All of the factors have been considered with regard to the claim, with the most relevant factors discussed below:

1) The breadth of claims: Claim 40 is directed to a method of treating anti-proliferative disorders such as cancer. This claim is also directed to use against the proliferation of parasites. In addition the claim is drawn towards the use against cardiovascular disorders linked to proliferation as well as to use as herbicides. This breadth of the claim is too broad and it is not supported by the specification. The claim encompasses treatment of any number of cancers by administering the instant compound. It is clear to a person skilled in this art that each cancer is distinct and varied in origin and distinct

in the way of manifestation and treatment. Moreover claim state that the compound which can be used for treating cancers can also be used against the proliferation of parasites. The parasite population is too broad and unlikely a single compound can be used against all the parasites. Moreover the claim state that the same compound which can be used for treating cancer and parasites can also be used for cardiovascular disorders and also can be used as herbicides. There is no support for this claim in the specification except that it can inhibit the enzyme kinases. It is known for a person skilled in the art that all these diseases have not been treated with a single compound as disclosed here. The breadth of the claim is too broad and it claims the treatment of disorders from different areas without any support from the specification.

2) The nature of the invention: The invention is drawn to the pharmaceutical compositions containing pyrrolo-pyrazines derivative having inhibitory activity to kinase enzymes which can be applied to the biological systems. This effect is linked to anti-proliferative effect which in turn encompasses the different areas like treatment of cancer, cardiovascular disorders and use as anti-parasites and herbicides.

3) The state of the prior art: The state of the art is underdeveloped for treating cancer and there is no known effective anticancer agent for all the cancers. There are compounds that treat a range of cancers but there is no single compound effective against a majority of cancers and it is contrary to our current understanding in oncology. Cancers could arise from a wide variety of sources, such as viruses like EBV, HHV-8, exposure to tobacco, radiation, genetic disorders and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different

organs and each organ has different methods of growth mechanism and hence treatment with a single compound would be ineffective. Even those that affect a single organ are often not generally treatable because of its diverse nature. For example different type of cancer can occur in different cells of the lungs such as Oat cell (small), giant cell, clear cells squamous cell and cancer can be adenocarcinoma or mesothelioma. The state of the art with respect to cardiovascular diseases is reasonable developed and various kind of treatments available including manipulating enzymes. With respect to the use of anti-parasites and herbicides the state of the art is medium and several compounds and compositions are known for treating parasites and as well use as herbicides. However the specification does not describe or support the use of the composition for treating all types of cancer, cardiovascular diseases also to use as anti-parasites and herbicides.

4) Amount of direction provided by the inventor: There is no guidance in the specification about the use of the composition for treating the different types of cancer. Also there is no direction in the specification about the use of the instant composition for treating cardiovascular diseases. In addition the details are lacking with regard to use of the composition as anti-parasites as well as to use as herbicides. It is not clear from the specification that the observation of inhibition of enzyme can be translated into treating all theses diseases.

5) The level of predictability in the art: The invention is directed to a method of treating anti-proliferative disorders such as cancer. This claim is also directed to use against the proliferation of parasites and use as herbicides. In addition the claim is drawn towards

the use against cardiovascular disorders linked to proliferation. It is known that any physiological phenomenon is considered variable and unpredictable and cancers are especially unpredictable because of their complexity in their nature. The treatment of one type of cancer could not be necessarily the same for the other type. The treatment of cardiovascular diseases or use as anti-parasite and herbicides are also unpredictable to certain extent because these also encompass the physiological phenomenon and hence tend to be unpredictable.

6) The existence of working examples: The working examples are lacking for the treatment of cancer, cardiovascular disease with the use of the instant composition. Moreover there are no working examples for preventing the proliferation of parasites and also for the use as herbicides. All the examples discuss the inhibition of kinase enzymes but fail to extrapolate this observation for treating disorders as mentioned above or use against parasites or to use as herbicides.

8) The quantity of experimentation: One skilled in the art would be required to undertake undue experimentation to make and/or use the invention as claimed. First the subject matter of the treatment of cancer is not established. It is not clear about methodology of the formulation and administration - since it varies at great extent depending upon the type of cancer under consideration. In addition the pharmacological carrier, dosage, route of administration, duration of treatment, etc also varies. Moreover for human treatment an appropriate animal model system has to be established to observe the efficacy and safety of the claimed compositions. The animal model may vary based on the type of cancer for treatment. Furthermore, when the

successful outcome is observed with the animal model it has to be optimized for treating human subjects. For treating cardiovascular diseases also dosages, formulations, efficacy and toxicity has to be established. For the use of instant composition as anti-parasites and also as herbicides entirely different set of parameters has to be established using different models with different experimentations. For each category one skilled in the art has to undertake a large quantity of experimentation to practice the invention as disclosed in the specification. Thus without undue experimentation one skilled in the art would not be able to practice this invention.

Claim Rejections - 35 USC § 102

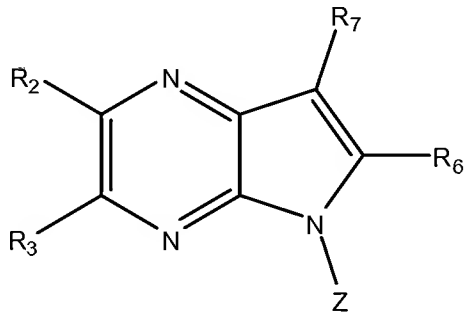
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-12, 14-20, 22, 23, 25, 26, 28-32 and 38-43 are rejected under 35 U.S.C. 102(e) as being anticipated by Picard et al US Patent 6,943,174.

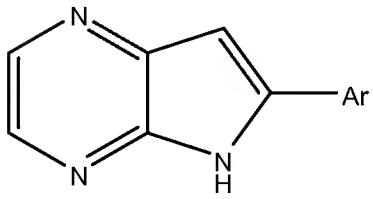
Claim 1, 2, 4-6, 8, 9, 16 -19, 22, 23, 25, 26, 28 and 30 are drawn to Pyrrolo – pyrazine derivatives with general formula(I). The structure of the compound do not comply with the standard structural formula as stated above in 112 rejection however examiner taken the position that the double bond is between the C atoms at the position

6 and 7. In addition, the claim 14 a dependent on claim 1, fails to describe the position for the group R as stated above in 112 rejection. Examiner taken the position that R group is a substitution in the aromatic cycle (aromatic cycle is in R6 position of formula 1) as stated in the claim 5.



Where R2, R3 and R7 can be H and R6 can be optionally substituted aromatic cycle Ar or an optionally substituted cycloalkyl aryl group.

Picard et al anticipates the core structure of the elected species.



Picard et al teaches the same substitution as claimed in the instant claims 1, 2, 4-6, 8, 9 and 16-18 (page 5 formula VI) with aromatic substitution at R6.

Claims 5, 7, 10, 13 14, 15, 17,19, 21, 22, 23, 25, 28, 29 and 31 are drawn to the property of the compound, various IC_{50} values (a unit for inhibitory activity) in addition to the structure of the compound. Since the compound anticipated by the Picard et al is

same as claimed in the instant invention the property of the compound would be the same and it is unseparable from the compound (See In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)) and hence it doesn't carry a patentable weight.

Claim 38 is drawn to pharmaceutical compositions comprising an effective amount of at least one derivative of claim 1 as active principle, in association with a pharmaceutically acceptable carrier. Picard et al anticipates the effective amount of compounds with pharmaceutically acceptable carrier (Column 35, Table of formulation).

Claim 41 is drawn to the pharmaceutical compositions of claim 38, administered in various forms e.g. orally, topically, by injection (intravenously, subcutaneously, intraperitoneally, or rectally). Claim 42 is drawn to the pharmaceutical composition of claim 41, for administration by the oral route comprising 100 to 1000 mg of active principle per dose unit, preferably 300 to 600 mg. Claim 43 is drawn to the pharmaceutical compositions of claim 41 under injectable forms, comprising 100 to 1000 mg of active principle preferably 300 to 600 mg, per dose unit. Picard et al anticipates the pharmaceutical compositions in various forms (Column 35 line 20-31 under formulations) and in various doses including the range of doses in the instant claims (Column 35 line 10 -19).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MANU MANOHAR whose telephone number is (571)270-5752. The examiner can normally be reached on Mon - Thu 9.00AM to 4.00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MANU MANOHAR
Examiner
Art Unit 4161

MM

/SREENI PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1617